# The Enigma of Desmoid Tumors

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## **Objective**

To analyze patients with recurrent extremity desmoids, in whom the surgical therapeutic option was either major amputation or observation.

## **Summary Background Data**

The biology and natural history of desmoid tumors are an enigma. These tumors invade surrounding structures and recur locally but do not metastasize. The morbidity of treating these tumors in the context of their relatively benign biology is uncertain.

#### Methods

Between July 1982 and June 1998, the authors treated and prospectively followed 206 patients with extremity desmoid tumors. All patients underwent standardized surgical resection, the surgical goal always being complete resection with negative margins. When tumors recurred, they were evaluated for reresection. Amputation was considered when resection was not possible because of neurovascular or major bone involvement, or in the presence of a functionless, painful extremity.

#### Results

During this period, 22 patients had disease that was not resectable without amputation. This was out of a total of 115

patients with primary disease and 91 patients with recurrent disease. All recurrences were local; in no patient did metastasis develop. In this group of 22 patients with unresectable disease, 7 underwent amputation and 15 did not. These 15 patients were followed, alive with disease, having no surgical resection. Four patients received systemic treatment with tamoxifen and nonsteroidal antiinflammatories, three received systemic cytotoxic chemotherapy, and two received both tamoxifen and chemotherapy. Six patients received no systemic treatment. The range of follow-up was 25 to 92 months. In all patients, there was no or insignificant tumor progression; in three patients who underwent observation alone, there was some regression of tumor. During follow-up, no patient has required subsequent amputation, and no patient has died from disease.

## **Conclusions**

In desmoid tumors, aggressive attempts at achieving negative resection margins may result in unnecessary morbidity. Function- and structure-preserving procedures should be the primary goal. In select patients, whose only option is amputation, it may be prudent to observe them with their limb and tumor intact.

Desmoid tumors are rare, slow-growing, histologically benign tumors. Despite their benign appearance, they are locally aggressive and invade surrounding structures, sometimes being classified as low-grade fibrosarcoma. At a cel-

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lular level, they lack the nuclear and cytoplasmic features of malignancy and have no metastatic potential. 1-4 Molecular studies of X-chromosome inactivation have confirmed that these lesions are the result of a clonal process, establishing that desmoids are neoplasms and not the product of an intense inflammatory fibrous reaction.<sup>3</sup> Desmoids occur in three general locations:

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- 1. The extremities (commonly around limb girdles or the proximal extremity) 2. The abdominal wall (commonly found in women,
- especially during and after pregnancy)

3. The bowel wall and mesentery (often associated with familial adenomatous polyposis).

Extremity tumors, because of their locally aggressive behavior, have a propensity for recurrent growth, resulting in local recurrence rates ranging from 24% to 77%. 4-8 Local recurrence rates for intraabdominal tumors are higher than those reported for extraabdominal tumors, ranging from 57% to 86% after complete resection. 9-11 Because of their anatomic location, they are a significant cause of complications and even death.

Despite these data, the natural history of desmoids remains poorly understood. Most studies have mingled intraand extraabdominal tumors as well as combined primary
and recurrent lesions, leading to conflicting reports regarding the biology and management of these tumors. 4-9,12-16
Further, their natural history is not well defined and is often
enigmatic. The purpose of this study was to analyze a highly
select group of patients with recurrent extremity desmoids
in whom the surgical therapeutic option was either major
amputation or observation. In particular, we report on the
natural history of a subset of these patients who have been
observed with their tumor intact.

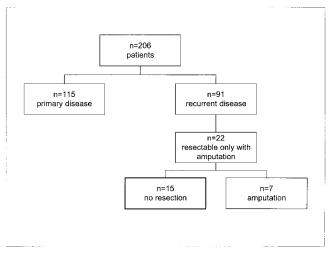
## **METHODS**

This study was performed by retrospectively identifying a subset of patients with desmoid tumors who were admitted and treated at Memorial Sloan-Kettering Cancer Center between July 1982 and June 1998. All patients underwent standardized surgical resection, the surgical goal always being complete resection, and were then prospectively followed. When tumors recurred, they were evaluated for reresection. Amputation was considered when resection was not possible because of neurovascular or major bone and joint involvement, or in the presence of a functionless, painful extremity. Patients underwent nonoperative treatment at the discretion of the treating physicians. This included radiation therapy, endocrine therapy, nonsteroidal antiinflammatories (NSAIDs), and cytotoxic chemotherapy. Pediatric patients (younger than 16 years) were excluded from this study.

Patient demographics, tumor characteristics, prior surgical resection margins, and the use of nonoperative treatment were analyzed. The resection margins of the tumor were assessed based on surgical findings (gross margin) and by pathologic evaluation (microscopic margin). Follow-up was based on clinical and radiologic data.

## Statistical Analysis

Local failure and recurrence-free survival were calculated from the time of the first surgical procedure. Follow-up time was calculated from the time of presentation with recurrence requiring amputation. Local recurrence was defined as occurring after a complete surgical resection, or the pres-



**Figure 1.** Distribution algorithm of 206 patients treated and followed with desmoid tumors of the extremity. Of these, 22 tumors were resectable only with amputation, and 15 patients underwent no resection and no amputation.

ence of clinically or radiographically appreciable disease after an incomplete surgical resection with grossly positive margins. Survival rates are reported for individual patients. No actuarial statistics were performed because of the small cohort number.

## **RESULTS**

We treated and prospectively followed 206 patients with extremity desmoid tumors between July 1982 and June 1998. During this time, 22 patients had recurrent tumors that were not resectable without amputation. This was out of a total of 91 patients with recurrent disease. All unresectable tumors were local recurrences, and metastasis did not develop in any patient. Within this group of 22 patients with unresectable disease, 7 underwent amputation and 15 did not (Fig. 1). All patients undergoing amputation had painful, functionless, or infected extremities. These were partly the result of recurrent desmoid tumor and partly of local complications of treatment.

## **Patient Characteristics**

The median age was 34 years (range 18 to 61 years). The age of the patient, as a continuous variable, or age younger than 30 years was not significant in determining local recurrence. The female:male ratio was 7:8.

#### **Tumor Characteristics**

The anatomic distribution of the tumors was six in the upper extremity and nine in the lower extremity. Tumor site did not influence the risk of developing local recurrence, nor the need for amputation. At the time of primary presentation for the first surgical procedure, one tumor (6%) was <5 cm,

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| Patient No. | Age | Gender | Anatomic Site | XRT<br>(cGy) | Systemic<br>Treatment | Follow-Up<br>Time (months) | Progress     |
|-------------|-----|--------|---------------|--------------|-----------------------|----------------------------|--------------|
|             |     |        |               |              |                       |                            |              |
| 1           | 27  | F      | Shoulder      | 6200         | T, chemo              | 37                         | PR           |
| 2           | 18  | M      | Buttock       | 5800         | N, chemo              | 39                         | PR           |
| 3           | 36  | M      | Knee          | 6000         | Chemo                 | 40                         | Unchanged    |
| 4           | 51  | M      | Shoulder      | _            | Chemo                 | 36                         | Unchanged    |
| 5           | 35  | M      | Hip           | _            | Chemo                 | 37                         | Unchanged    |
| 6           | 55  | M      | Elbow         | _            | T, N                  | 28                         | Unchanged    |
| 7           | 41  | F      | Buttock       | _            | T, N                  | 48                         | Slow ↑       |
| 8           | 48  | F      | Thigh         | _            | Т                     | 25                         | Slow ↑       |
| 9           | 41  | F      | Shoulder      | _            | Ν                     | 42                         | Unchanged    |
| 10          | 19  | F      | Upper arm     | 5600         | _                     | 25                         | PR           |
| 11          | 31  | F      | Upper arm     | _            | _                     | 35                         | $\downarrow$ |
| 12          | 34  | M      | Thigh/groin   | _            | _                     | 92                         | ↓/↑          |
| 13          | 24  | M      | Buttock       | _            | _                     | 37                         | Unchanged    |
| 14          | 19  | F      | Knee          | _            | _                     | 29                         | <b>↓</b>     |
| 15          | 60  | М      | Thigh/groin   | _            | _                     | 33                         | Slow ↑       |

Table 1. SUMMARY DESCRIPTION OF 15 PATIENTS WITH RECURRENT DESMOID TUMORS\*

seven tumors (47%) were 5 to 10 cm, and seven tumors (47%) were >10 cm. At the time of consideration of amputation, all tumors exceeded 10 cm. The size of the primary tumor was not significant in determining local recurrence. All of these tumors were deep to the fascia at initial and recurrent presentation.

## **First Surgery**

At the initial surgical procedure for primary tumor, 11 patients had grossly negative margins and 4 had grossly positive margins. Of the 11 with complete gross resection, 7 had microscopically negative margins and 4 had microscopically positive margins. In the 15 patients, the median time to first local recurrence was 17 months, similar to the time for other patients with recurrent desmoids. Four of these patients had a second local recurrence, and one patient had a third local recurrence.

#### Postrecurrence Follow-Up

The 15 patients who did not undergo resection were given nonoperative treatment at the discretion of the treating physician. These data are summarized in Table 1. Four patients received external beam radiation ranging from 5800 to 6200 cGy. All four had some response to radiation treatment: the tumors shrank over an 8- to 24-month period after treatment. Four patients received systemic treatment with tamoxifen or NSAIDs, three received systemic cytotoxic chemotherapy, and two received both tamoxifen and chemotherapy. Of these nine patients, five had some response to treatment. Six patients received no treatment other than observation. In all patients, there was no or insignifi-

cant tumor progression (Figs. 2 through 4); in three receiving no treatment other than observation, there was minimal regression. The range of follow-up was 25 to 92 months. During follow-up, no patient has required subsequent amputation, metastasis has not developed in any patient, and no patient has died from the disease.

#### DISCUSSION

Desmoid tumors are histologically benign neoplasms that are difficult to treat because of their clinical infiltrative growth pattern and high propensity for local recurrence. Although several prognostic factors for recurrence have been identified, treatment recommendations for these tumors are often contradictory. Part of this inconsistency is because of our lack of understanding of the natural history of this disease. In this study, we report on 15 patients with tumors that were unresectable without major amputation. This highly selected group of patients did not undergo amputation or resection, and there was no or insignificant tumor progression with their tumor intact. During followup, no patient has required subsequent amputation, and no patient has died from the disease.

Most data regarding desmoids have come from analyses that include intra- and extraabdominal tumors as well as combined primary and recurrent lesions, leading to conflicting reports regarding the biology and management of these tumors. 4-9,12-15,17-19 In a recent study, we examined a homogeneous population of patients with primary extraabdominal desmoid tumors followed at a single institution, and we were not able to identify any representative risk factors predicting local recurrence. 4

<sup>\*</sup> These patients did not undergo amputation/resection and were followed with tumor and limb intact. Chemo, chemotherapy; N, nonsteroidal antiinflammatory drugs; T, tamoxifen; PR, partial response.

Figure 2. Axial T1-weighted magnetic resonance imaging scan of shoulder in patient 3. The right image was taken 12 months after the left one. This patient underwent no treatment, and the tumor remained stable during this time.



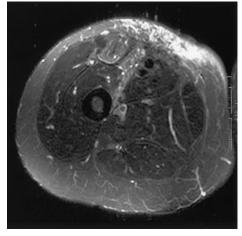


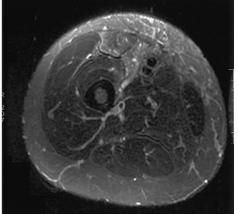
+ 12 Months

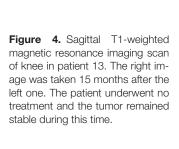
Surgical resection is the primary treatment modality for extremity desmoid tumors. Because of the infiltrative nature of these tumors, local recurrence rates after wide local excision may be high. Although several authors have reported a significantly increased risk of local recurrence in patients with positive or close resection margins, <sup>13,20–22</sup>

others have found no differences in local recurrence rates between patients with positive or negative margins. 4,12,23,24 The precise association of the surgical resection margin with local recurrence is difficult to evaluate: most reports include only a small number of patients, group together intraabdominal and extraabdominal tumors as well as recur-

Figure 3. Axial Fat Sat magnetic resonance imaging scan of thigh in patient 7. The right image was taken 23 months after the left one. The patient underwent no treatment, and the tumor remained stable during this time.











+ 15 Months

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rent and primary disease, or include patients who have received multiple forms of treatment, including radiation therapy, surgery, and chemotherapy.

Of the studies analyzing primary disease only, Easter and Halasz<sup>20</sup> reported local recurrence in one of four patients with a negative margin and three of six patients with a positive margin; in three of three patients with a close or unknown margin, local recurrence developed. Pritchard et al<sup>14</sup> reviewed 34 patients with primary disease who underwent surgery only. Of these, 2 of 13 patients with a negative resection margin developed local recurrence, compared to 1 of 2 with a positive margin and 9 of 19 with a close or unknown margin. Posner et al<sup>13</sup> reviewed 138 patients with desmoid tumors, including those with recurrent disease and intraabdominal tumors, and identified a positive resection margin as well as presentation with recurrent disease to be independent factors determining local recurrence on multivariate analysis. In contrast to these findings, Miralbell et al<sup>12</sup> reported local recurrence in only 4 of 18 patients with a positive resection margin and no local recurrence in 3 patients with tumor margins within 1 to 2 mm, giving a local control rate of 81% at 5 years. In our recent study<sup>4</sup> of patients with primary tumors, we found that the status of the resection margin had no influence on local recurrence, and patients had an overall local control rate of 75% at 5 years. Some of the patients with positive margins were given adjuvant radiation therapy.

Thus, part of the enigma of these tumors is that although it is intuitively wrong, leaving desmoid tumor behind as a positive margin may not be associated with the risk of subsequent local recurrence.<sup>4</sup>

The natural history of desmoid tumors is one of unpredictable, usually slow, and locally invasive growth. Conversely, some of these tumors may stop growing and indeed may even regress. Anecdotal observations from several studies regarding the management of tumors with positive margins with observation alone and conservative treatment of recurrent disease support the role of limited radical surgery in decreasing the risk of local recurrence. Rock et al<sup>15</sup> followed 68 patients with desmoid tumors with observation only. In 60 of the 68 patients, the tumor remained stable with minimal symptoms during a follow-up of 6.3 years. In six patients the tumor became smaller, and in only two patients did the tumor grow.

Reresection for the treatment of recurrent disease is advocated by most because it results in a cure rate similar to that of primary resection. Reitamo et al<sup>23</sup> showed that the recurrence rate after a second or third resection was equal to or lower than the recurrence rate after primary resection. Posner et al<sup>13</sup> reported on 33 patients who underwent reresection after local recurrence: 28 (85%) remained free of disease with a median follow-up of 70 months. In our most recent study, local recurrence developed in 24 of 105 patients with primary disease. Of these, 22 underwent reresection and 19 remained free of disease with a median follow-up of 67 months (range 10 to 146 months). Two

patients in whom a second local recurrence developed were free of disease after a second reresection, and the one patient with a third local recurrence was alive with disease.

Radiation therapy has been shown to improve local control of desmoid tumors, both in the adjuvant and primary settings. 12,14,21,22,24 In contrast, other reports have shown little benefit with its use, 15 and sometimes worse results with radiation therapy than with surgery alone. 14,15,25 All of these series, however, include a small number of patients reviewed in a retrospective fashion, with no surgical controls. Overall, the local control of these tumors with the use of radiation therapy is similar to that obtained by surgical management alone. Nevertheless, radiation therapy may offer some benefit in providing local control in patients with gross residual disease. The most consistent results for complete control have been seen in patients receiving doses >6000 cGy; complete regression of tumor may require up to 2 years. In our current study, there was no difference in symptoms or progression of tumor in those treated with or without radiation, although this question obviously cannot be adequately answered with such a small and highly selected group.

Several systemic agents have also been used in the treatment of desmoid tumors. The use of hormonal therapy for the treatment of these tumors is predicated on the association of estrogen levels with the growth of desmoid tumors. There is a higher incidence of these tumors, especially in the abdominal wall, during or soon after pregnancy or while taking oral contraceptives. 26-30 There have also been reports of spontaneous regression of desmoids after menopause and after oophorectomy. 20,23 In addition, desmoids may be associated with an increased number of estrogen receptors and antiestrogen binding sites, although not in all tumors.31,32 Several anecdotal reports have suggested that the use of various antiestrogen agents may result in regression of these tumors. <sup>26,28,33–35</sup> Despite the theoretical use of endocrine therapy for desmoid tumors, these reports are primarily anecdotal, include a small number of patients, and have response rates of approximately 50%.

Nonsteroidal antiinflammatory drugs have also been used in the treatment of desmoid tumors. In the literature, the overall response rate of NSAID therapy alone is approximately 50%.28 Responses to combinations of therapies, including antiestrogens, NSAIDs, vitamin K, warfarin, and vitamin C, have also been reported. 28,33,36 Cytotoxic chemotherapeutic agents have also been used for the treatment of desmoid tumors. These include doxorubicin-based regimens and, more recently, low-dose combination methotrexate and vinblastine. Although several reports of efficacy have been documented, the use of potentially toxic systemic therapy for the treatment of localized disease should be examined in terms of possible benefit versus detriment. 37-41 In our current study, there was no difference in symptoms or progression of tumor in those treated with or without systemic therapy, although again this question obviously can-

not be adequately answered with such a small and highly selected group.

Desmoid tumors are enigmatic. Their natural history appears to be that of slow, locally invasive growth, although some tumors stop growing and others regress. Achieving negative margins during resection should always remain the goal, even though the presence of gross or microscopic residual disease has not been proven to influence the survival rate. Although the addition of radiation or systemic therapy has not been shown to improve prognosis or functional outcome, there may be a role for these adjuvant treatments in selected patients. Adjuvant radiation has been suggested to diminish local recurrence and should be used selectively, especially in margin-positive tumors. It is undetermined why some tumors continue to grow and others can be followed for long periods without any subsequent problem. The risk of resection or aggressive radiation or chemotherapy for recurrent disease, resulting in significant complications, needs to be weighed against the risk of observation alone or leaving residual disease after resection. Whether radiation or chemotherapy affects overall outcome is unclear, and again the risk of complications needs to be weighed against the risk of observation alone. Thus, when treating desmoid tumors, aggressive attempts at achieving negative resection margins may result in unnecessary complications. Function- and structure-preserving procedures should be the primary goal. In select patients whose only option is amputation, it may be prudent to observe them with their limb and tumor intact.

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## **Discussion**

Dr. Edward M. Copeland, III (Gainesville, Florida): I thank Dr. Brennan for pointing out to us that certainly not all patients who have recurrent desmoids require an amputation.

Desmoid tumors are indeed an enigma because responses have been reported from multiple treatment regimens, most of which Dr. Brennan has outlined for us in his report. In fact, as he stated, 10 of the 15 patients in this series received some form of nonsurgical treatment that is reported in the literature to work on these tumors. We have been proponents at the University of Florida of the addition of radiation therapy to the resected tumor bed for large, recurrent lesions and/or those that have positive surgical margins. Likewise, lesions surrounding critical structures in an extremity will often shrink with preoperative radiation therapy, making sacrifice of these critical structures unnecessary.

I still attempt to get pathologic negative margins and use intraoperative frozen section as a guide. I agree with the authors, however, that extremity function should not be sacrificed to obtain negative margins.

As I recall in Dr. Murray Brennan's original report from his sarcoma database to the American Surgical Association several years ago, he thought that margin status was not particularly important as an indicator of future local recurrences. With maturation of that database, I think he has changed his mind.

For recurrent desmoids, margin status is less meaningful, since the histology of the lesion can be difficult to differentiate from the scar of the original excision. Consequently, I have liberally used radiation therapy as an adjunct to resection of recurrent desmoids of the trunk and extremity, especially large lesions and those close to the critical structures.

To illustrate the radiosensitivity of at least one of these lesions, I would like to present the case of a 25-year-old female with an unresectable desmoid of the left shoulder girdle. She was treated with 4000 cGy in a 4-week period 17 years ago, with complete resolution with radiation therapy alone. To date there is no recurrence

My questions to Dr. Brennan and Dr. Lewis are the following: Do you recommend any form of treatment for desmoid tumors other than surgical resection?

When you are lucky enough to do the initial resection on a large desmoid, do you attempt to obtain pathologically negative margins? Do any of your observed philosophies elucidated here apply to intraabdominal desmoids associated with Gardener's syndrome, particularly those that might encompass the superior mesenteric artery and require resection of major portions, if not all, of the small bowel?

Dr. R. Daniel Beauchamp (Nashville, Tennessee): In analyzing the data from your overall experience, it has been apparent that a positive microscopic margin does not have an influence on recurrence rates. But I'm just wondering whether that is true for a grossly positive margin.

The second question is, what adjuvant treatment do you currently advocate, if any, for these tumors, and does that recommendation differ for recurrences?

And then the third question is perhaps more philosophical. What is known of the biology of these lesions that allows them to invade tissue planes, and then, in your long-term follow-up, to stop growing and in some cases regress spontaneously and not to metastasize? What is the difference between these tumors and the more invasive aggressive sarcomas that will metastasize?

Dr. Leonard T. Furlow Jr. (Gainesville, Florida): I would just like to ask—in parallel with other fibrous tissue, benign tumors, what is the effect of pressure? And what is the effect of steroid injection on these lesions?

Dr. ROGER R. PERRY (Norfolk, Virginia): Dr. Brennan, I enjoyed your paper very much. But can you really say that margins don't matter? In other words, if you ignored margins in everyone and just grossly removed disease, would your local recurrence rate be even higher than you have demonstrated so far?

President Griffen: While you are coming up to close, you mentioned several patients with upper extremity tumors that involved the brachial plexus. Have you had occasion to relieve a patient with an arm that hurts all the time with therapy? Or do you do anything to try and control the transferral? Do you try to do anything to relieve the symptoms on the nerves? You may close.

Dr. Jonathan J. Lewis (Closing Discussion): At the outset I can inform you that neither Dr. Brennan nor myself have given up doing operations on these patients.

Addressing specific questions: Dr. Copeland, in terms of response to radiation therapy, we also have observed that some patients do respond. That response has been variable and, in some patients, may last, whereas in others, the tumor may come back. Other than resection, in selected patients in particular, in patients who are margin-positive, we do use radiation.

We certainly do try, in all patients, to obtain a negative margin. And we try and do that, both in terms of the gross disease and the microscopic margin. We do not use frozen section because, in our experience, frozen section is very difficult to interpret.

Your final question regarding abdominal desmoids—do the same principals apply? And the answer to that is yes. And the rationale for that is that in our experience with some 20 to 25 patients with abdominal desmoid tumors, 3 of them have, through treatment, eventually had total enterectomies. So we have 3 patients who are alive now but are totally dependent on TPN because of direct complications of treatment. So that in selected patients in whom we predict resection is going to be very difficult, we may

well start initially by not doing an operation and by following them

In answer to Dr. Beauchamp's questions, again, margin is important. In general, in soft tissue sarcoma, there is a correlation between margin and local recurrence. Again, in soft tissue sarcoma, that correlation between marginal local recurrence does not translate into an impact on overall or disease-specific survival.

Extrapolating that to our data with desmoids, while in the group of primary patients that we have previously studied the difference between positive and negative margin was not apparent, those patients with positive margins had had selective additional treatment such as radiation therapy. So, again, it is our philosophy to try and resect these patients with negative margins.

The adjuvant therapy that we do use is selective radiation. Again, we don't have good data for that, and this begs the question of doing a randomized prospective trial. And, certainly, the new American College of Surgeons oncology group would be the perfect setting to do such a randomized prospective trial and, hopefully, answer that question.

Dr. Beauchamp's final question, which is the biology of these tumors—and, again, this is what is truly intriguing, and perhaps that is the platform for a far better understanding of correlation between genotype and phenotype. Because, clearly, when one looks at these tumors under the microscope they are not malignant. However, their behavior in terms of locally transgressing tissue plans and behaving locally like a cancer certainly begs the question that at least some of the genes within these tumors must represent

the same or similar ones to cancer without going the whole way. Because, again, they don't metastasize.

In answer to Dr. Furlow's question, we don't know the exact effect of pressure, as such, on these tumors. We do know that there can be a causal or an associated relationship with trauma. And, certainly, with abdominal wall, and women in particular who have undergone operations—but then again, there are reports of certain athletes who have been playing contact sports, in particular the sports of football in this country and rugby in England, several reports of such patients who have been told to stop playing, and the tumors have either stopped growing and/or regressed.

We do not know the effect of direct injection of steroid.

Again, getting to the last question on the issue of margins, just to keep on reinforcing that, we do believe that margins are important, and we certainly do try and do an operation, especially the first time around where we can resect these patients with negative margins.

The final question relating to the brachial plexus, in patients who are symptomatic, we will do everybody we can to treat them, again philosophically weighing the morbidity of the treatment *versus* the outcome in that patient. But clearly when that patient is symptomatic and in the absence of any other effective treatment such as in the seven patients we presented, a patient who has involvement of the brachial plexus, who is symptomatic, certainly would be a candidate for surgical resection. And in that particular instance, that would be an amputation.